Claims

1. A method for screening a collection of nucleic acid molecules for a desired property of the nucleic acid or of a (poly)peptide encoded thereby, comprising the steps of
   (a) automated picking of a collection of cells containing the collection of nucleic acid molecules by means of a first robot;
   (b) automated lysis of the cells by means of a second robot;
   (c) automated separation of the cellular DNA from the cell debris by means of a second robot;
   (d) optionally automated separation of endotoxins from the DNA by means of the second robot if the cells are bacteria;
   (e) automated transfection of cells with the DNA obtained in step (c) or, if the cells are bacteria, obtained in step (d) by means of a third robot; and
   (f) automated screening for the desired property by means of a fourth robot.

2. The method according to claim 1 wherein the collection of nucleic acid molecules is a gene library or a collection of clones.

3. The method according to claim 1 or 2 wherein the nucleic acid molecules are genomic DNA or cDNA molecules or RNAi oligonucleotides.

4. The method according to claim 2 or 3 wherein the gene library is an expression cDNA gene library, preferably a eukaryotic gene library, a human gene library is particularly preferred.

5. The method according to any one of claims 1 to 4 wherein the cells in step (a) and/or step (e) are mammalian cells, insect cells, yeast cells or bacteria.

6. The method of claim 5 wherein the bacteria are Gram-negative bacteria.

7. The method of claim 6 wherein the Gram-negative bacteria belong to the species E. coli.

8. The method of any one of claims 1 to 7 wherein at least one of the steps (a) to (f) is carried out in microtitre plates.

9. The method according to claim 8 wherein all steps (a) to (f) are carried out in microtitre plates.

10. The method according to claim 8 or 9 wherein the microtitre plates have bar codes.

11. The method according to any one of claims 1 to 10 wherein the first robot is characterised by
    (a) a digital image processing system for collecting the plated bacteria,
    (b) a working station with a grip arm for microtitre plates for transferring the microtitre plates between the processing stations,
    (c) a separation module having one or more heads with needles for picking the plated single colonies and for placing them into the microtitre plates,
    (d) integrated product processing stations for cleaning the needles between the working steps and replicating the placed single colonies in the microtitre plates and
    (e) a computer-based bar code identification and tracking system.

12. The method of any one of claims 1 to 4 wherein the lysis is an alkaline lysis.

13. The method of any one of claims 1 to 12 wherein the second robot is characterised by
    (a) a conveyor road transport system combined with grip arms for the microtitre plates for reloading the products and for transferring the microtitre plates between the product processing stations,
    (b) product processing stations integrated into the transport system, particularly centrifuges, pipetting automats, shakers and incubation places for incubation at different temperatures,
    (c) a sensor technology for the detection of product positions as well as for the detection of errors,
    (d) a software for the interlaced handling of several processes which are in the machine for a continual production process and

(e) a computer-based bar code identification and tracking system, preferably with an internal product tracking containing a time stamp function for the interlacing of time-critical sub-processes.

14. The method according to any one of claims 1 to 13 wherein the separation of the cellular DNA in step (c) is carried out with silica particles.

15. The method according to claim 14 wherein the silica particles are magnetic silica particles.

16. The method according to any one of claims 1 to 15 wherein the separation of the endotoxins in step (d) is carried out with endotoxin-binding particles, which are preferably magnetic endotoxin-binding particles.

17. The method according to any one of claims 1 to 15 wherein the separation of the endotoxins in step (d) is carried out by precipitation with SDS/isopropanol.

18. The method according to any one of claims 14 to 16 wherein the DNA bound to silica particles is further purified by washing with acetone.

19. The method according to any one of claims 1 to 18 wherein the transfection of cells in step (e) is mediated by calcium phosphate, electroporation or by lipofactors.

20. The method according to any one of claims 1 to 18 wherein the transfection is carried out by means of DNA-binding magnetic biocompatible micro-particles.

21. The method of any one of claims 1 to 20 wherein the third robot is characterised by

(a) a conveyor road transport system combined with grip arms for microtitre plates for reloading the products and for transferring the microtitre plates between the product processing stations,

(b) product processing stations integrated into the transport system, particularly pipetting stations, shakers and incubation places and an incubator for culturing the transfectants,

(c) a sensor technology for the detection of product positions as well as for the detection of errors,

(d) sterile overpressure ventilation to prevent contaminations of the cell cultures,

(e) a software for the interlaced handling of several processes which are in the machine for a continual production process and

(f) a computer-based bar code identification and tracking system, preferably with an internal product tracking containing a time stamp function for the interlacing of time-critical sub-processes.

22. The method of any one of claims 1 to 21 wherein the fourth robot is characterised by

(a) a system for determining the fluorescence, luminescence or colour reactions from cell culture assays,

(b) a pipetting station with a grip arm for microtitre plates for transferring the microtitre plates from the incubator to and between the product processing stations,

(c) processing places for adding and withdrawing cell culture media or reagents and incubation in the incubator and

(d) computer-based bar code identification and tracking system.

23. The method according to any one of claims 1 to 21 wherein the fourth robot is characterised by

(a) a digital image processing system and image acquisition system for determining the cell morphology, fluorescence and/or luminescence

(b) a pipetting station with grip arm for microtitre plates for transferring the microtitre plates from the incubator to and between the product processing stations,

(c) processing places for adding and withdrawing cell culture media or reagents and incubation in the incubator and

(d) a computer-based bar code identification and tracking system.

24. The method according to any one of claims 1 to 23 wherein the automated screening is a functional screening.

25. The method according to claim 24 wherein the functional screening is a screening for an enzymatic, pharmacological or therapeutic property.

26. The method according to claim 14 or 25 wherein the functional screening is a screening for activation or suppression of a reporter system or wherein the screening is a screening for the function of a secreted protein.

27. The method according to any one of claims 1 to 26 wherein 2, 3 or 4 robots are arranged in a conveyor road.

28. The method according to any one of claims 1 to 27 wherein a DNA, (poly)peptide or a transfectant containing the same, which has been identified in the screening process is purified or isolated.

29. The method according to any one of claims 1 to 28 which moreover comprises the improvement of the binding properties of the (poly)peptide encoded by the DNA identified or isolated in the screening process according to any one of claims 1 to 28, comprising the steps of
    (a) identification of the binding sites of the (poly)peptide or its binding partner by site-specific mutagenesis or chimeric protein studies;
    (b) molecular modelling of the binding site of the (poly)peptide and of the binding partner; and
    (c) modification of the (poly)peptide in order to improve the binding specificity or the affinity of the binding.

30. The method according to claim 29 wherein the modification in step (c) is a reproduction of the (poly)peptide by peptidomimetics.

31. The method according to any one of claims 1 to 28 wherein the (poly)peptide as a leading structure is further modified in order to obtain
    (i) a modified site of action, a modified spectrum of activity, a modified organ specificity, and/or
    (ii) an improved activity, and/or
    (iii) a decreased toxicity (an improved therapeutic index), and/or
    (iv) decreased side effects, and/or
    (v) a delayed onset of the therapeutic action, of the duration of the therapeutic effect and/or
    (vi) modified pharmacokinetic parameters (resorption, distribution, metabolism or exretion), and/or

(vii) modified physico-chemical parameters (solubility, hygroscopic properties, colour, taste, odour, stability, state), and/or
(viii) improved general specificity, organ/tissue specificity, and/or
(ix) optimised application form and route

by

(i) esterification of carboxyl groups, or
(ii) esterification of hydroxyl groups with carboxylic acids, or
(iii) esterification of hydroxyl groups to e.g. phosphates, pyrophosphates or sulfates or succinic acid semiesters, or
(iv) formation of pharmaceutically acceptable salts, or
(v) formation of pharmaceutically acceptable complexes, or
(vi) synthesis of pharmacologically active polymers, or
(vii) introduction of hydrophilic moieties, or
(viii) introduction/exchange of substituents in aromates or side chains, change of the substituent pattern, or
(ix) modification by introduction of isosteric or bioisosteric moieties, or
(x) synthesis of homologous compounds, or
(xi) introduction of branched side chains, or
(xii) conversion of alkyl substituents to cyclic analogues, or
(xiii) derivatisation of hydroxyl groups to ketals or acetals, or
(xiv) N-acetylation to amides, phenylcarbamates, or
(xv) synthesis of Mannich bases, imines, or
(xvi) transformation of ketones or aldehydes to Schiff's bases, oximes, acetals, ketals, enolic esters, oxazolidines, thiozolidines or

combinations thereof.

32. The method for the manufacture of a pharmaceutical composition comprising the steps of the method according to any one of claims 23 to 31 and, moreover, formulating of the substance obtained with a pharmaceutical acceptable carrier or diluent.

Summary

The present invention relates to a method for screening a collection of nucleic acid molecules for a desired property of the nucleic acid or of a (poly)peptide encoded thereof, comprising the steps (a) automated picking of the cell collection containing the collection of nucleic acid molecules with a first robot; (b) automated lysis of the cells with a second robot; (c) automated separation of the cell DNA from the cell debris with a second robot; (d) optionally automated separation of endotoxins from the DNA with the second robot if the cells are bacteria; (e) automated transfection of the cells with the DNA obtained in step (c) or, if the cells are bacteria, with the DNA obtained in step (d) with a third robot; and (f) automated screening for the desired property with a fourth robot. Moreover, the invention relates to methods for the enhancement of the binding properties of the (poly)peptide identified by the of the screening method of the invention or encoded by the DNA identified and isolated and a method for the production of a pharmaceutical composition on the basis of (poly)peptides which can be obtained with the method of the invention and moreover the formulation of the substance obtained with a pharmaceutically acceptable carrier or dilutent.